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Radiation is an Important Component of Multimodality Therapy for Pediatric Supratentorial Non-Pineal Neuroectodermal Tumors

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ABSTRACT

Title: Radiation is an Important Component of Multimodality TherapyPediatric Supratentorial Non-Pineal Neuroectodermal Tumors

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Purpose: We reviewed a historical cohort of pediatric patients with supratentorial primitive neuroectodermal tumors (sPNET) in order to clarify the role of radiation in the treatment of these tumors.

Patients and Methods:

Fifteen children <18 years old with non-pineal sPNETs diagnosed between 1992 and 2006 were identified. Initial therapy consisted of surgical resection and chemotherapy (CT) in all patients and up-front radiotherapy (RT) in 5 patients. Five patients had RT at the time of progression and five received no RT whatsoever. Kaplan-Meier estimates of overall-survival (OS) were then calculated.

Results: The median follow-up from diagnosis for all patients was 31 months (range 0.5-165) and for surviving patients was 49 months (range 10-165). Of the 5 patients who received up-front RT, all were alive without evidence of disease at a median follow-up of 50 months (range 25-165). Only 5 of the 10 patients who did not receive up-front RT were alive at last follow-up. There was a statistically significant difference in overall survival between the group of patients that received up-front RT and the group that did not (P=0.048). Additionally, we found a trend toward a statistically significant improvement in overall-survival for those patients that received gross total resections (P=0.10).

Conclusions: Up-front radiotherapy and gross total resection may confer a survival benefit in patients with sPNET. Local failure was the dominant pattern of recurrence. Efforts should be made to determine patients most likely to have local failure exclusively or as a first recurrence in order to delay or eliminate cranio-spinal irradiation (CSI).

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INTRODUCTION:

Supratentorial primitive neuroectodermal tumors (sPNET) were first described in 1973 and are defined as poorly differentiated, embryonal, predominantly pediatric tumors that arise in the cerebrum or suprasellar region, comprising approximately 2-3% of all childhood brain tumors (1). Since their discovery, the traditional consensus has been that sPNETs simply represent a slight, although considerably more aggressive, variation on their infratentorial cousins—medulloblastomas. But it is slowly becoming apparent that these tumors are very distinctive entities with critical differences as compared to medulloblastomas. This re-evaluation is largely being driven by studies which seem to suggest that sPNETs have a unique biology. However, it was the knowledge regarding their clinical behavior, gained since their discovery, that first hinted at these comparative biological differences.

Epidemiology and Diagnosis: Compared to medulloblastomas, sPNETs arise approximately 1/10th as frequently, comprising only 3 to 7% of all primary pediatric CNS lesions (2). Within the pediatric age group, 80% of these lesions are diagnosed before age 10, 65% before age, and 25% before age 2 (3). To date, there has been no reported sex preference in terms of diagnosis. In adults, sPNETs occur even less frequently, , although, adult patients appear to have increased survival relative to their pediatric counterparts (4).

Of interest, there appears to be a subset of pediatric patients who received cranio-spinal irradiation as part of their treatment for hematological malignancies who later develop high grade glial tumors, including sPNET, as a consequence of their prior irradiation (5); such secondary sPNETs can also arise after treatment for other primary CNS neoplasms, again as a consequence of neuraxis radiation. Some patients in whom these secondary sPNETs develop have a tumor predisposing genetic condition such as a Retinoblastoma or Neurofibromatosis. For others, however, there is no obvious genetic lesion that might help to explain the development of a secondary malignancy in response to initial therapy for prior disease (6).

The primary distinction between medulloblastomas and sPNET is, of course, location of occurrence—infratentorially in the former and supratentorially in the latter. More specifically, sPNETs tend to predominantly occur in the cerebrum or suprasellar region. Less frequently, sPNETs can originate in the retina, pineal gland, deep paraventricular region, diencephalon, and basal ganglia. Case reports have also made mention of sPNET presentation in the leptomeninges without evidence of a primary cerebral lesion, although this is exceedingly rare (7). Indeed, it may simply represent a microscopic primary with early dissemination. Metastasis at presentation, however, is not uncommon in sPNETs, with approximately 13-27% of patients having some degree of dissemination at diagnosis (8).

sPNET and medulloblastomas share a common staging system, the Chang Metastasis Staging System. Using this system, an M0 lesion is defined as a primary lesion without evidence of subarachnoid or hematogenous spread. An M1 lesion is one where CSF studies reveal tumor cells. M2 disease evidences gross nodular seeding in the intracranial subarachnoid space or ventricular system distant from the primary site, whereas M3 disease presents with gross nodular seeding in the spinal subarachnoid space. Finally, any extra-neural disease is classified as M4 (9).

The presentation of sPNETs can very widely both within and between different populations. For adults and older children, signs of increased intracranial pressure are often seen, including headache, nausea, and vomiting. Less frequently, patients may present with seizures or focal neurological deficits (2). If leptomeningeal dissemination has already occurred, patients may suffer from cranial nerve palsies, encephalopathy, or spinal cord symptoms. When compared to older age cohorts, the youngest patients have

a distinctive subset of symptoms with irritability, anorexia, lethargy, or enlarging head circumference tending to predominate (10).

Initial diagnostic work-up will invariably include both CT and MR imaging. CT often demonstrates a well-circumscribed, usually hemispheric mass that can contain both areas of calcification and necrosis. Although less common, CT may also show evidence of intra-tumoral hemorrhage. MR imaging will show significant heterogeneity, with hypointense portions representing hemosiderin deposition and calcification. On T1-weighted MR imaging, hyper-intense regions represent areas of hemorrhage, while on T2-weighted scans, these hyperintense foci are often cystic components. Unlike gliomas, for sPNETs, peri-tumoral edema is relatively absent (11). Overall, while imaging may be suggestive of diagnosis, more definite conclusions require histological examination.

Unfortunately, definitive diagnosis of sPNETs remains a significant challenge to clinicians, since they are almost histologically indistinguishable from medulloblastoma. Current WHO criteria define sPNETs as Grade IV tumors comprised of at least 90% undifferentiated or poorly differentiated neuroepithelial cells. This differs slightly from the commonly accepted definition in United States, where any embryonal tumor composed of small round blues cells located above the tentorium, regardless of location, presence of focal differentiation, extent of resection, or metastatic stage, is considered a sPNET (12). Additionally, it is recognized that sPNETs have the ability to differentiate along multiple pathways, including neuronal, astrocytic, ependymal, muscular, and melanocytic.

Because of the paucity of histological markers specific for sPNETs, diagnostic criteria rely almost exclusively on their location and their relative lack of differentiation.

However, even this definition is troublesome for pathologists as it is oftentimes the case that sPNETs are dedifferentiated to the point where it is difficult to distinguish them from "round" or "small cell" glioblastoma variants (13). And in very young children, it is important to decide whether polyphenotypic sPNETs with epithelial membrane antigen and smooth muscle actin might actually represent CNS rhabdoid tumors.

Biology: But while the diagnostic picture for sPNETs remains muddled, researchers are increasingly coming to realize that these tumors have a distinctive biology that separates them from their infratentorial counterparts. Initial karyotypic studies in a series of 22 pediatric sPNETs demonstrated the presence of both double minute structures and a high level of gene amplification. More surprisingly was the finding that in eight of the 22 cases, the karyotype was normal (3). The remaining 13 cases showed complex karyotypes involving mostly structural changes, including interstitial deletions, partial chromosome gains, and chromosomal translocations. The cytogenetic abnormalities that recurred with the greatest frequency included deletions or translocations in chromosome 10q22-26 (3 of 13 cases) and translocations that involved chromosome 6q21-25 (2 of 13 cases). Interestingly, the tumor in one individual evidenced a translocation involving chromosome 6q25 and chromosome 13q14. The tumor suppressor RB1 resides on chromosome 13q14 and this translocation may somehow involve constitutional inactivation of this gene.

Comparative Genomic Hybridization (CGH) studies completed on approximately 16 sPNET patients revealed a greater frequency of imbalances than was seen on traditional karyotypic analysis (14,15,16). These data demonstrated that sPNETs have

significant differences in the pattern and frequency of DNA copy number changes as compared to medulloblastomas. One of the more common genetic abnormalities in medulloblastomas is chromosome 17 loss. This was not apparent in any of the sPNETs examined. A characteristic isochromosome 17, resulting from the gain of chromosome 17q and loss of 17p, is seen in approximately 40% of medulloblastomas. For sPNETs, only one case of isochromosome 17 has been reported. However, more recent work using CGH arrays and FISH analysis have shown that a fraction of sPNETs do indeed have abberations on chromosome 17 (17). Additionally, epigenetic modifcations in breakpoint cluster regions are often seen in medulloblastomas, appearing in approximately 30% of those examined. Again, these alterations have not been seen in any of the sPNETs characterized to date (18).

Although specific changes common to medulloblastomas were not seen in sPNETs, a study of approximately 17 pediatric sPNETs using CGH demonstrated a higher frequency and greater complexity of DNA copy number changes when compared to medulloblastomas (19). Approximately 70% of tumors evidenced genomic imbalances, with a median of four changes per tumor. Of those changes, the majority involved entire chromosomes, whereas partial chromosomal imbalances were seen in 37% of tumors. In these 17 cases, the vast majority of alterations involved chromosomal loss rather than gain. The most common loss, seen in approximately 50% of these cases, was loss of chromosome 4q. Other, less frequently seen, regions of deletions occurred in distal areas of 9p, 13q, 14q, and 10q. The tumor suppressors that putatively reside in many of these regions have yet to be characterized, however, losses in regions of chromosome 10q, which include tumor suppressors such as PTEN and DMBT1, were

seen in approximately 25% of sPNETs examined (20). And although chromosomal gains were far less frequent in sPNETs, those seen tended to mirror ones already identified in medulloblastoma. Most notable were gains at chromosome 7 and the q arm of chromosome 1. Again, less frequently observed are gains on chromosomes 9qter, 13 and 17. More recent work has shown that a gain of chromosome region 20q13.33 is seen in a not insignificant number of sPNETs. This corresponds to a region frequently amplified in glioblastoma that results in the constitutive overexpression of the CD95 decoy receptor (17).

While karyotypic and CGH analyses have tended to support the notion that sPNETs are neoplasms distinct from medulloblastoma, microarray studies looking at expression differences have gone a long way towards confirming this idea. One of the seminal works in support of this notion was published by Pomeroy, et al (21). Having analyzed approximately 99 patient samples that included sPNETs, medulloblastomas, atypical teratoid/rhabdoid neoplasms, and malignant gliomas, the authors concluded that there were distinctive pathways that were differentially expressed in medulloblastomas compared to sPNETs. Specifically, the transcription factors ZIC1 and NSCL were overexpressed in medulloblastomas but not sPNETs. Based on this finding, the authors argued that these two tumor types might have different cells of origin, with the original idea being that they both arose from cerebellar granule cells. But the question remains—what pathways, by way of increased activation, are critical to the development of sPNETs?

The Shh-Gli pathway is one pathway crucial in normal cerebral development that may play a role in sPNET tumorigenesis. In murine models, the Gli proteins (Gli1-Gli3),

downstream effectors of Shh, exert strong mitogenic effects on nestin positive neocortical precursor cells in the subventricular zone (22). Some studies have shown that, in a significant fraction of sPNETs, Gli1 mRNA is overexpressed (23). Additionally, in a small series of sPNETs examined by IHC, there appeared to be increased expression of the n-MYC oncoprotein, itself a known downstream target activated by the Shh signaling pathway (24). These findings have recently been confirmed by expression microarray data that found n-MYC overexpression in approximately 30% of sPNETs examined (25). Finally, missense mutations in the PTCH locus, a gene whose protein product is known to antagonize Shh signaling, have been identified in 3 in a series of 8 pediatric sPNETs examined (26).

Another pathway critical in neurogenesis that may play a role in sPNET development is the Notch-Hes signaling cascade. The Notch proteins, four of them have been identified, are large, membrane spanning receptors for ligands such as Jagged and Delta that are themselves membrane bound. Upon ligand binding, the Notch receptor is cleaved and the intracellular fragment translocates to the nucleus where it serves as a transcription factor instrumental in the activation of the Hes family proteins (27). Hes proteins themselves then negatively regulate transcription factors such as hASH1. Evidence abounds for the involvement of the Notch-Hes pathway in both proliferation and differentiation. Not surprisingly, aberrant Notch signaling is often seen in neoplastic lesions. Most notably, in certain variants of T-cell leukemia a translocation results in constitutive activation of the gene (28). It has been shown that the Notch2 mRNA is overexpressed in sPNETs compared to medulloblastoma and control cerebellar cells (29). The overexpression of Notch2 in these tumors appears to result from genomic

amplification of the Notch2 gene locus. Compellingly, knockdown of Notch2 expression in a sPNET cell line successfully decreased its proliferative capacity.

A final pathway where increased activity may play a role in the development of sPNETs is the fabled Wnt cascade. Wnt signaling plays a crucial role in many of the canonical steps in tumorigenesis, including differentiation, proliferation, and invasion. The cascade is initiated by binding of Wnt to the transmembrane protein Frizzled. This causes the activation of the Dishevelled family of proteins, ultimately leading to the cytosolic stabilization, and eventual translocation to the nucleus, of β-Catenin. Once in the nucleus, β-Catenin serves to transcriptionally activate a variety of oncogenes, including c-MYC and n-MYC (30). While not conclusive by any means, there is some suggestion that the Wnt cascade might play a role in a fraction of sPNETs. In a series of only 4 sPNETs, one tumor evidenced a mutation in β -Catenin that resulted in increased stabilization and thus nuclear accumulation of the protein (31). The increased stability of β-Catenin was a result of a mutation in its protein degradation targeting sequence. Although earlier it was suggested that Shh signaling might be responsible for the increased expressin of N-myc in sPNETs, it is equally plausible that this type of β-Catenin mutation might be responsible for the observed alteration in N-myc protein levels.

So while activation of the above oncogenic pathways appear to be important in sPNETs, a further discussion of tumor suppressors that, when inactivated, might play equally important roles in the development of these lesions, is necessary. Firstly, there is some evidence to suggest that, at least in the case of adult sPNETs, mutational inactivation of the classic tumor suppressor, p53, might play an etiologic role. p53 is, of

course, involved in DNA repair, cell cycle arrest, and the induction of apoptosis; it is often referred to as the "guardian of the genome" (32). In a study involving 11 adult sPNETs, mutations in p53 were observed in six cases (33). In stark contrast, in the 28 cases of pediatric sPNETs examined, only one was found to have a p53 mutation (34). Secondly, there is some evidence to suggest that upwards of 20% of sPNETs have deletions of the tumor suppressor DMBT1 (Deleted in Malignant Brain Tumors-1), a membrane bound glycoprotein containing multiple scavenger receptor cysteine-rich (SRCR) domains separated by SRCR-interspersed domains (SID) (35). It is proposed that DMBT1 plays a role in both immune defense and epithelial differentiation. Thirdly, there is a case report of a germline mutation in the mismatch-repair gene PMS2 leading to the development of sPNETs in two consanguineous twins (36). Fourthly, Pfister, et al have recently discovered, using CGH array technology, that a significant number of sPNETs (7 of 21 examined) have either heterozygous or homozygous deletion of the CDKN2A locus. This locus is responsible for the production of two critical cell-cycle inhibitors, p16INK4A and p14ARF; the former acts by deactivating various cyclin-CDK complexes, while the latter functions to promote p53 expression by inhibiting MDM2. And finally, and more surprisingly, is the possible role of the tumor suppressor MSH2 in sPNET tumorigenesis. MSH2 is frequently mutated in hereditary non-polyposis colon cancer (HNPCC) and, like PMS2, plays a crucial role in mismatch repair mechanisms. Deletions of MSH2 result in accelerated tumor formation in knock-out mice. However, in sPNETs, it appears that MSH2 expression is increased (25). This is consistent with observations made in glioblastoma and medulloblastoma. At this time, the significance of this overexpression of a known tumor suppressor in these neoplasms is unclear.

Despite the significant advances in the knowledge of sPNET biology, the treatments for these tumors largely center on the use of protocols originally designed to target high-risk medulloblastomas.

Treatment and Prognosis: There are two major challenges that have made the identification of significant prognostic factors and the optimization of treatment strategies difficult in cases of sPNET: 1) the relative difficulty in distinguishing these lesions from the myriad other cerebral neoplasms and 2) their relative paucity. Indeed, in the ongoing COG trial 99701, several patients enrolled that had thalamic tumors that were originally thought to be sPNETs, upon surgical biopsy were found to have glioblastoma multiforme. Because of the difficultly posed in identifying these tumors pathologically, it must be remembered that any clinical trial involving sPNET patients may have limited applicability given inter-institutional variation in the peculiarities of diagnosis.

Because they are infrequent, clinical trials devoted exclusively to sPNET are relatively few in number. One of the earliest randomized controlled trials was the CCG 921 trial (37). This trial involved 55 patients, ages 1.5 to 19.3 years. Patients were randomized to one of two arms. In the first arm, patients received cranio-spinal irradiation followed by eight cycles of 1-(2-chloro-ethyl)-3-cyclohexylnitrosourea (CCNU), vincristine, and prednisone. The second arm involved two cycles of 8-in-1 chemotherapy followed by RT and then eight additional cycles of 8-in-1 chemotherapy. The 8-in-1 regimen included methyprednisone, vincristine, carmustine, procarbazine, hydroxyurea, cisplatin, cytarabine, and cyclophosphamide.

For all patients in the study, three year Kaplan-Meier estimates of overall survival (OS) and progression free survival (PFS) were 57% and 47%, respectively. There was no statistically significant difference in either OS or PFS between the two treatment arms, although, not unsurprisingly, the more chemotherapy intensive regimen had greater toxicity. Univariate analysis revealed that both metastasis at diagnosis and age adversely affected PFS. For M0 patients, 50% had no progression at 3 years, while all patients that were M2-M4 had progressed. For patients that were 1.5-2 years of age at diagnosis, 25% had not progressed by year 3 versus 50% of those that were older than 3.

The next major prospective trials evaluating treatment options for sPNET patients were the German HIT 88/89 and HIT 91 trials (38). Here 63 pediatric patients (ages 3-18) were enrolled after surgery, with 21 patients having gross total resections of their tumors. Patients were then randomized to two different treatment arms—one involved pre-irradiation chemotherapy with two cycles of ifosfamide, etoposide, methotrexate, cisplatin, and cytarabine; the second arm involved post-irradiation chemotherapy consisting of eight cycles of cisplatin, vincristine, and lomustine. It was recommended that radiation be administered to the entirety of the neuraxis to a dose of 35.2 Gy, with a boost of 20 Gy to the primary site. Despite these recommendations, seven patients were treated with 54.0 Gy limited to the site of the primary lesion.

Again, OS was approximately 48% at 3 years. Thirty-eight patients had progressed, with local failure in 27 of these patients. There was a dramatic difference in survival between patients that received the recommend dose and volumes of radiotherapy and those that did not. The PFS for adherent patients was 49.3% at 3 years compared to 6.7% in those patients that received sub-optimal radiotherapy. From this, the authors

concluded that cranio-spinal irradiation (CSI) was necessary to at least 35 Gy with boost to the primary site of at least 20 Gy.

The first results that arrived from the German trials concerned only children above age 3. Unfortunately, and especially for those under 3 years of age, there are significant long-term toxicities, in particular neuropsychological morbidity, associated with the use of radiotherapy, especially cranio-spinal irradiation (CSI) (39-41). Concerted recent effort has therefore been devoted to alternative therapeutic regimens that eliminate radiation, delay radiotherapy, or reduce radiation dosages or fields. It was with these concerns in mind that Timmermann, et al evaluated the survival data on 29 children ages 3-37 months that had been enrolled in the HIT-SKK87 and HIT-SKK92 trials (42).

In the earlier trial, HIT-SKK87, the children were divided into two arms depending upon the extent of resection and the presence of metastases. Low risk patients received maintenance chemotherapy until RT was administered after age 3, while high-risk patients received intensive induction chemotherapy followed by a maintenance regimen until RT was administered, again after age 3. In cases of progression or recurrence, RT was delivered immediately. For those in the later trial, HIT-SKK92, three cycles of methotrexate based chemotherapy were given after surgery. If recurrence or progression occurred before 18 months, an experimental chemotherapeutic regimen was recommended, while if these events occurred after 18 months, RT was administered.

Unfortunately, OS and PFS rates of 17.2% and 14.9%, respectively, were extremely disappointing, confirming age younger than 3 as a negative prognostic indicator. Still more troubling was the finding that of the 15 children that had received

no RT, only one survived. The administration of RT was a statistically significant predictor of OS and PFS. The authors concluded that the omission of RT jeopardized survival, even if intensive chemotherapy was administered in its stead. In their discussion, they recommended that any delay in RT be limited to 6 months for children in this age group. However, this study has been criticized on the grounds that, of the 15 patients that refused RT, 14 had early disease progression, suggesting that the no RT group may have been sicker, on average, than those that had received RT (43).

However, a recent Canadian retrospective study of pediatric sPNET patients came to a conclusion similar to that of Timmermann, et al (44). This study collected information on sPNET patients less than 19 years of age who had been treated at thirteen centers throughout Canada. In total, sufficient data was obtained on 48 patients. For these patients, four-year survival stood at approximately 37%. The study confirmed that very young patients had a worse OS than their older counterparts. Most significantly, the authors found that the use of RT and chemotherapy significantly improved OS. For those receiving radiation, the 4-year survival stood at 48.2% compared to 8.3% for those who had not received radiation; for those receiving chemotherapy, four-year survival was 43% compared to 12.5% survival for those that had not received chemotherapy. The authors concluded that radiation should remain an important component in any treatment strategy for sPNETs.

The importance of radiation as a component of multi-modal treatment has once again and most recently been challenged by the results of the Head Start (HS) I and II trials (45). These prospective trials enrolled 43 children with a median age of 3.1 years. It should be noted that a significant percentage of the children, 47%, were less than 36

months of age. All patients first underwent a maximally safe surgical resection. Patients in HSI and those with localized disease in HSII then underwent five cycles of treatment with vincristine, cisplatin, cyclophosphamide, and etoposide. Patients in HSII with disseminated disease had methotrexate added to the above regimen. Assuming disease stability, patients then received a single cycle of high-dose myeloablative chemotherapy followed by autologous stem cell rescue. Five-year event free survival (EFS) and OS were 39% and 49% respectively and compared favorably to historical controls, some of which were mentioned above. Perhaps most importantly, 60% of those surviving were alive without exposure to RT. Surprisingly, in this study, age was not a significant prognostic factor, nor was extent of disease or degree of surgical resection.

However, it should be noted that these findings regarding prognostic factors were atypical. The majority of studies have concluded that the region in which the sPNET arises is predictive of outcome, although it has not always been clear whether specific regions portend better or worse outcomes. For instance, historically, it was assumed that lesions arising in the pineal region carried a worse prognosis than non-pineal tumors. Early retrospective studies, examining a total of 18 children suffering from pineal sPNETs, found that 17 had rapidly progressive disease and died within 2 years of diagnosis (46). However, recent data supports an opposite conclusion. In a sub-analysis of prospective CCG data on 25 children with pineal sPNETs, including 8 infants, Jakacki, et al found a 3-year PFS and OS for children over 18 months of age of 61% and 73%, respectively (47). These outcomes, when compared to non-pineal sPNETs in a similar age cohort, are impressive and the improvement has been attributed to the increasingly common use of multi-modal therapy to treat patients with sPNETs. Unfortunately, these

advances do not seem to translate into improved survival for children with pineal sPNETs under 18 months.

As we've mentioned, age, whether with pineal or non-pineal lesions, has shown itself to be a robust predictor of outcome. A POG study looking at children with pineal sPNETs confirmed the COG findings (48). For patients less than 18 months, progressive disease developed relatively rapidly and responded poorly to radiotherapeutic interventions. The same trends hold true for younger patients with non-pineal lesions. In the CCG study, for patients age 19 to 36 months, all eventually succumbed to progressive disease. A French Society of Pediatric Oncology study looked specifically at infants suffering from sPNETs (49). The French study examined data from 25 patients less than 5 years of age who were treated with chemotherapy alone and found a relatively dismal 2 and 5-year survival rate of 30% and 14%, respectively. One obvious caveat is that these patients received chemotherapy exclusively, so it's unclear whether, if salvage RT had been used, it would've produced survival rates commensurate with the older children's. What needs to be clarified regarding age is whether the worse prognoses that are being consistently found are a result of a difference in sPNET biology and behavior in this age group or an artifact of ginger treatment standards, with sub-optimal dosing of chemotherapy and radiotherapy given to avoid possible side effects. This dilemma has yet to be resolved.

A further factor with possible prognostic implications is the question of extent of resection. Oftentimes, sPNETs will arise in eloquent areas of the cerebral cortex, making gross total resection extraordinarily difficult; pineal region sPNETs also pose significant surgical challenges. A study using CCG data found that large pre-operative tumors were,

not unsurprisingly, more likely to be associated with post-operative volumes of 1.5 cm^2 or greater (50). Less than 1.5cm^2 of residual tumor was seen in approximately 52% of patients examined. Most significant was the finding that post-operative volumes less than 1.5cm^2 carried with it a post-operative survival at 4-years of approximately 40%, whereas those with residual volumes greater than the 1.5 cut-off had a dismal 4-year survival of approximately 14%. Older trials have tended to confirm this earlier finding (51). By comparison, in the more recent German HIT trials, resections were performed to the safest extent possible, with only 38% achieving gross total resection as assessed by imaging. However, there was not statistically significant difference in survival between those that had received sub-total versus gross-total surgeries. More recent data argues for the relative prognostic insignificance of extent of resection. The Canadian retrospective study previous mentioned as well as the Heat Start trials also examined the prognostic significance of extent of resection. In the Canadian study, 45% of patients had gross-total resections. They found there to be no significant relationship between extent of resection and survival. The Head Start trial divided patients into four groups, depending upon the extent of resection: biopsy, partial resection, sub-total resection, and gross-total resection. Again, their analyses revealed no relationship between extent of resection and overall survival. It can be convincingly argued that, as the ability of both chemotherapy and radiation to obtain local control increases, the relative importance of the extent of resection will tend to recede. This may be why we see, in the more recent studies, the extent of resection no longer acting as a significant prognostic variable.

The presence or absence of metastatic disease may also be of prognostic importance in sPNET patients. The CCG study already mentioned showed that, for those

patients with metastatic disease, the survival rate was nearly 0% (37). A retrospective, multi-institutional study of 22 patients with sPNET, five of whom had disseminated disease at the time of diagnosis, found that all five of those patients had died by 5 years after diagnosis (51). From these data, it would appear that metastasis at diagnosis negatively impacts outcome. One could argue that the cranio-spinal irradiation and chemotherapeutic regimens used in these studies were insufficient to eradicate metastatic foci. More interestingly, however, is the conclusion from the Head Start trials that metastasis at diagnosis did not portend significantly worse outcomes. Again, these trials used intensive, myeloablative chemotherapy regimens. This finding was confirmed in the German HIT trials which, again, found no impact of disease dissemination at diagnosis on later outcomes. The idea that these intensive regimens, chemotherapy in the Head Start and CSI in the German regimen, might achieve better systemic control could help to explain the relative unimportance of dissemination at diagnosis.

Finally, we would like to discuss the importance of radiation therapy in the treatment of sPNETs and its significance as a prognostic factor. One of the critical, and still unanswered questions, is the extent to which field size is important in achieving durable remission and enhancing survival. Although cranio-spinal irradiation (CSI) has become the standard of care, prospective data supporting its use is lacking. Earlier, prospective studies where patients received either CSI, whole-brain, or simply involved field therapy evidenced no clear relative benefit for any one option (52, 53). One of the more comprehensive of these retrospective studies was completed by Dirks, et al in which they compiled clinical data on 36 patients that had received multimodal treatment for sPNETs, with a median age of diagnosis of 35 months (7). They found that there was

no statistically significant difference between those who did receive CSI and those who simply received whole brain irradiation (p=0.24). This is in contrast to Paulino, et al who reported on 25 patients with sPNETs, with a quite divergent age range (12 months-32 years) (54). They found that 5-year survival for those patients that had received CSI was 47%. This was dramatically different when compared to those that had received whole brain or focal field RT only; for these patients, 5-year survival was 12% and 0%, respectively. Similarly, the German HIT trial on patients older than 3 years of age found CSI to be a crucial component of any successful sPNET treatment.

Questions of proper radiation dosing are also critical. Again, in the German HIT trial, any major deviations from defined radiotherapeutic protocols resulting in a significant survival decrement. Major deviations were defined as a primary site dose of less than 54 Gy or a craniospinal dose of less than 35 Gy. For instance, local doses of at least 54 Gy resulted in a 3 year PFS of 44.7%, while doses lower than this limit had a PFS of only 10%. In looking at CSI, doses above 35 Gy resulted in a 5-year PFS of 49.3% compared to 0% for those receiving a dose below this threshold. Attempts have been made to increase both CSI and primate site doses, most notably by Prados, et al at UCSF (55). This prospective study, which included approximately 25 medulloblastomas and 11 sPNETs, used hyperfractionation to increase doses to the primary site to 72 Gy with a reduction in doses to the cranio-spinal axis down to approximately 30 Gy using 1Gy dose per fraction. Unfortunately, while local control was adequate, there were a significant number of distant failures, indicating, as in the German HIT Trial, that reduction in CSI dose can compromise long-term survival. Additionally, no further benefit seems to have been achieved with increased local dosing. Strategies that are still

under exploration include the use of radiotherapy in conjunction with possible radiosensitizing agents, namely carboplatin. Carboplatin is a platinum-based chemotherapeutic agent introduced in the late 1980s with a much more favorable side-effect profile when compared to Cisplatin. The idea is that the radiosensitization will allow for reduced radiation dosages. Currently, COG 99701 is attempting to determine whether the addition of carboplatin will enhance outcomes in patients with high-risk medulloblastomas and sPNETs. Eventually, a phase III trial will begin with patients randomized to receive either radiotherapy alone or radiotherapy with concurrent carboplatin administration.

SUMMARY AND STATEMENT OF PURPOSE/AIMS:

Treatment for sPNETs requires a multi-modality approach that includes chemotherapy, surgery, and radiotherapy (RT). Results of prospective and retrospective studies with either intentional or unintentional deviations from standard radiotherapeutic protocol demonstrate reduced survival in patients not receiving standard-dose CSI (36 Gy) (38, 56, 57). However, the Head Start trials, which examined a patient population with a median age of 3.1 years, shows that treatment with high-dose chemotherapy alone followed by stem cell rescue allows for a reduction or elimination of radiation without adversely impacting overall survival (45). Current Children's Oncology Group (COG) Protocols classify sPNETs with high-risk medulloblastomas and thus call for treatment that involves standard dose CSI.

In light of this uncertainty over the role of radiation, we performed a historical cohort study to evaluate its utility in pediatric patients with sPNET treated at the University of California, San Francisco (UCSF). We sought to determine whether there was any evidence supporting delay, elimination, or reduction in field size or dose of radiation.

MATERIALS AND METHODS

Nineteen consecutive children <18 years old with non-pineal sPNETs diagnosed between December 1992 and December 2006 who received surgery at UCSF were identified. Four patients with inadequate follow-up (FU) were excluded, leaving 15 evaluable patients (Table 1). Inadequate FU was defined as lack of any information following surgery at UCSF, resulting from patients who did not reside locally and were lost-to-follow-up soon after their tumor resection, despite our concerted efforts to locate them. The median age at diagnosis was 3.1 years (range 0.2–12) and 33% were males. All patients were staged using spine MRIs with and without gadolinium and CSF cytology. Initial therapy consisted of surgery and chemotherapy (CT) in all patients and RT in 5 patients. Surgical intent was to achieve gross total resection (GTR) whenever possible. The extent of surgery was determined by reviews of the operative reports and postoperative radiologic studies. The most common chemotherapeutic regimen consisted of cisplatin, etoposide, cyclophosphamide, and vincristine; 2 patients received high-dose CT with autologous stem cell rescue. RT regimens consisted predominantly of external beam radiotherapy (EBRT) to the tumor bed with the addition of CSI in certain patients delivered at the discretion of the treating physician. The use and timing of RT was

determined by the treating Radiation Oncologist and largely based on the patient's functional status, age, and physician preference. The choice between CSI and focal RT was made at the discretion of the Radiation Oncologist and was heavily influenced by the age of the patient, as those younger than three years of age were more likely to receive focal RT than CSI.

All statistical analyses were performed using Statistica V 6.0 and StatXact-8. Kaplan-Meier methods were used to calculate overall survival (OS). Progression Free Survival (PFS) was calculated by defining the date of progression as the first mention of progression in imaging reports. All P values were determined using the exact log rank test and are two-tailed. Significance was defined as a P-value < 0.05. OS was defined as the time period between resection and death or date last known alive.

RESULTS

Patient characteristics are summarized in Table 1. The median follow-up from resection for all patients was 31 months (range, 0.5-165) and for surviving patients was 49 months (range, 10-165). All patients presented with non-pineal, supra-tentorial lesions. Only 2 of 15 patients presented with disseminated disease (M+) at diagnosis. In keeping with the observed sPNET demographics, 7 of the 15 patients were less than 3 years of age.

As part of their initial therapy, 5 patients received upfront RT, with total doses ranging from 50.4 to 72 Gy (Table 2A). Of the 5 patients with upfront EBRT, 4 received CSI with doses ranging from 23.4 to 36 Gy. Notably, all of the patients who received

upfront RT were alive without evidence of disease at a median follow-up of 50 months (range, 25-165).

Of the 10 patients who did not have up-front RT, 5 received it as salvage therapy at the time of progression. Of those 5, all experienced local failure either as the first or sole site of recurrence (Table 2B). Three of these salvage patients received EBRT with doses ranging from 54-57.6 Gy. In addition, one patient received brachytherapy using permanent Iodine-125 seeds and one patient received both EBRT and Iodine-125 seeds. Three of the patients who received salvage RT were alive without evidence of disease at last follow-up, 33, 102, and 111 months after diagnosis. Of the 5 patients who did not receive any RT either up-front or as salvage, 2 were alive at last follow-up (Table 2C). However, follow-up for these patients was comparatively short at 10 and 28 months. Of the 3 patients that died of disease, 1 had local and 1 had disseminated failure at the time of progression; an additional patient died 14 days after initial resection. Overall, only 5 of the 10 patients who did not receive up-front RT were alive at last follow-up. There was a statistically significant difference in overall survival between the group of patients that received up-front RT and the group that did not (P=0.048; Fig. 1).

Regarding Progression Free Survival (PFS), we found that for those patients who had received up-front radiation, none had progressed as of last follow-up. This is in sharp contrast to the group that did not receive up-front RT in which 8 out of 10 patients progressed, with a median time to progression of 6.5 months (range, 0-26).

In examining the RT fields utilized in the 10 patients who received RT (5 at diagnosis and 5 at progression), 5 had CSI and 5 had focal field only. Of the 5 patients who received CSI, none of the 4 who received radiation as part of up-front therapy

progressed; of note, 2 of these patients received standard dose of 36 Gy whereas 2 patients received reduced dose of 23.4 Gy. The single patient who received CSI (23.4 Gy) as salvage therapy died of his disease. Of the 5 patients whose RT consisted of focal field only, all were under 3 years of age and 4 were alive without evidence of disease at follow-up times ranging from 33-111 months after diagnosis. One patient died of her disease 31 months after diagnosis.

Children younger than 3 years with sPNETs have a particularly poor prognosis. Our cohort included 7 patients less than 3 years of age at diagnosis; five of these young children were alive and NED at last FU (range 3-111 months after diagnosis). Four of these 5 surviving infants received RT as part of their treatment, all consisting of focal field only (1 as part of initial therapy and 3 as salvage).

Finally, within our cohort, 8 of 15 patients had gross-total resections. For those receiving GTRs, one patient died at 31 months, with the remainder still alive and NED at median follow-up of 48 months (range, 25-165 months). Of the 7 patients receiving incomplete resections, 4 died at 0.5, 3, 5, and 21 months; three remain alive at last follow-up of 10, 50, and 111 months. After stratifying for up-front RT versus salvage or no RT, we found a trend towards an improvement in overall-survival for those patients that had received GTRs (P=0.10).

DISCUSSION

Traditionally, the treatment of sPNETs has involved surgery coupled with various chemotherapy and radiation regimens. Because of its significant morbidity, especially when administered to the entire cranio-spinal axis, attempts have been made to eliminate,

delay, or limit radiotherapy. Unfortunately, such trials have shown decidedly mixed results.

Our study attempted to ascertain the importance of radiotherapy in the treatment of children diagnosed with sPNETs. Despite the relatively few patients in our retrospective analysis, we feel that several points can be made. First, up-front radiotherapy does appear to offer a statistically significant improvement in OS in this study. This is consistent with the findings of Timmermann, *et al.* in their recent prospective study (38). However, our conclusion must be tempered by the obvious presence of a significant confounding variable. Among patients who did not receive up-front RT, 3 of the deaths occurred very soon after resection, with the decision not to give RT possibly related to a compromised clinical condition. As such, it is possible that these patients were significantly sicker on average than the patients in the up-front group. Indeed, when we eliminate the child who died soonest after resection (2 weeks), the resultant P value is 0.10, above the value of statistical significance. An additional potential concern is that, of the 7 children younger than 3 years of age, 6 were in the group that did not receive up-front RT. Since children under 3 have historically had a worse prognosis, this could represent a significant confounding variable. However, 4 of these 6 children remain alive at last follow-up and therefore we view confounding findings secondary to age as likely negligible in this study. The same caveats clearly apply to our data on progression. While our results for PFS suggest a benefit for up-front RT versus delayed RT, radiographic imaging was not systematically and uniformly acquired for all patients to assess progression, diminishing the strength of these findings.

We must also mention that re-grouping these patients by whether they received RT at all instead of the timing of RT is equally informative. With this grouping we find that 8 of 10 children that had RT are NED at the time of last follow-up compared with 2 of 5 children that never received RT. Either grouping is clinically instructive, but both share the same aforementioned limitations

Despite a small number of patients, patterns of failures are instructive. Eight patients progressed, all among children who did not receive radiation up-front. Five of these 8 failures were M0 at initial diagnosis and presented with local failure as the sole or first site of recurrence. This is consistent with results from the German HIT Trials where approximately 71% of patients had localized treatment failure. Given these data, one could hypothesize the existence of a subset of patients with tumors that have a decreased potential for metastatic spread. For these patients, focal irradiation following reduced-dose CSI or perhaps even without CSI in selected cases may be a feasible strategy. Alternately, since all patients received chemotherapy, one might argue that, in a subset of these patients, the regimen was sufficient to eliminate micrometases but was inadequate for primary tumor control.

In instances where field size was limited, our experience is encouraging as 3 of 4 M0 patients who received only focal RT are, as of last follow-up, without evidence of disease. However, given the small sample size, it is impossible to make explicit recommendations regarding which patients might benefit from a reduction in field sizes. However, we do believe that these data, at the very least, provide a strong rationale for the initiation of a larger randomized controlled trial designed to determine which patients might benefit from either a reduction in dose or complete elimination of CSI.

Finally, it does appear that, even after controlling for radiotherapy timing, there is a trend towards improved OS with more extensive resections. This is consistent with previously published results, but in contrast to a recent Canadian retrospective analysis that suggests that OS does not correlate with extent of resection (7,35,50). We believe a larger cohort of patients might help to determine the exact nature of the relationship between degree of resection and survival.

Overall, our data are consistent with the goal of maximal resection of these tumors in children and argues that RT plays a very important role in adjuvant treatment. Ultimately, a prospective trial considering survival and neuropsychological sequelae and comparing various chemotherapy-radiation regimens may be required to finally establish a standard of care specific to patients with this deadly tumor.

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Table 1: Patient Characteristics and Treatment Details

Patient characteristics	**Number of Patients**
Median age (range)	36 months (2-144)
Sex M:F	5:10
CNS disseminations: M0	3
M+	2
Radiation therapy: Up-front	5
At time of recurrence	5
None	5
Extent of resection: Gross total resection	8
Incomplete resection	7

Table 2A: Patients receiving radiation as component of initial treatment

Pt#	Age	Stage	Extent of Resection	Primary Tumor Dose (Gy)	CSI Dose (Gy)	Chemo	Pattern of Failure	OS (months)	Status
1	34	M0	GTR	50.4	0	Mafosphamide, Cisplatin, Cyclophos, VCR, Etoposide	No failure	48	NED
2	48	M0	GTR	72.0	36	Procarbazine, CCNU, VCR	No failure	165	NED
3	60	M0	GTR	55.8	23.4	CCNU, VCR, Cisplatin	No failure	80	NED
4	60	M0	GTR	55.8	36	Carboplatin, VCR, Cyclophos	No failure	25	NED
5	144	M0	STR	59.4	23.4	CCNU, VCR, Cisplatin	No failure	50	NED

Abbreviations: GTR: gross total resection; STR: subtotal resection; CSI: cranio-spinal irradiation; FU: follow-up; NED: no evidence of disease; VCR: Vincristine; MTX: Methotrexate, TMZ: Temozolomide.

Table 2B: Patients receiving radiation as component of salvage treatment

Pt#	Age	Stage	Extent of Resection	Tumor Dose (Gy)	CSI Dose (Gy)	Chemotherapy: Agents used for each patient	Pattern of Failure	PFS	OS	Status
6[§]	2	M0	GTR	57.6	0	Cyclophos, Etoposide, VCR, Cisplatin, MTX	Local followed by CNS dissemination	7	31	DOD
7	14	M0	GTR	54.0	0	Cyclophos, Etoposide, VCR, Cisplatin, TMZ, Lenalidomide, Accutane, CCNU	Local	9	33	NED
8	21	M+	STR	90.0*	0	MTX, Cyclophos, VCR, Cisplatin, Etoposide	Local	26	111	NED
9	24	M0	GTR	36.0 + 80*	0	Cyclophos, VCR, Etoposide	Local	7	102	NED
10	72	M0	STR	54.0	23.4	Cyclophos, Etoposide, VCR, Cisplatin, TMZ, Procarbazine, CCNU	Local	6	21	DOD

*Brachytherapy using I-125 permanent seeds
[§] Patient received stem cell rescue

Abbreviations: GTR: gross total resection; STR: subtotal resection; CSI: cranio-spinal irradiation; FU: follow-up; NED: no evidence of disease; DOD: dead of disease; VCR: Vincristine; MTX: Methotrexate, TMZ: Temozolomide, Cyclophos: Cyclophosphamide, PFS: Progression Free Survival, OS: Overall Survival.

Table 2C: Patients who never received radiation therapy

Patient	Age	Stage	Extent of Resection	Primary Tumor Dose (Gy)	CSI Dose (Gy)	Chemo	Pattern of Failure	Progression Free Surival (months)	Overall Surv.	Disease Status at Last FU
11	12	M0	STR	0	0	Cisplatin, Etoposide, Cyclophos	Concurrent local and CNS disseminati on	3	4	DOD
12	24	M0	GTR	0	0	Cisplatin, Etoposide, Cyclophos, VCR	No failure	No progression	28	NED
13	36	M0	STR	0	0	Carboplatin, VCR, Cyclophos	Local	1	5	DOD
14[§]	36	M0	STR	0	0	MTX, VCR, Etoposide, Cisplatin, Cyclophos, Thiotepa, Carboplatin	No failure	No Progression	10	NED
15	120	M+	STR	0	0	Ifosphamide Carboplat Etoposid	NA*	0	0.5	DOD

Abbreviations: GTR: gross total resection; STR: subtotal resection; CSI: cranio-spinal irradiation; FU: follow-up; NED: No evidence of disease; DOD: dead of disease; VCR: Vincristine; MTX: Methotrexate, TMZ: Temozolomide, Cyclophos: Cyclophosphamide.

* Patient died 14 days after resection, before complete disease status evaluation could be conducted.

[§] Patient received stem cell rescue

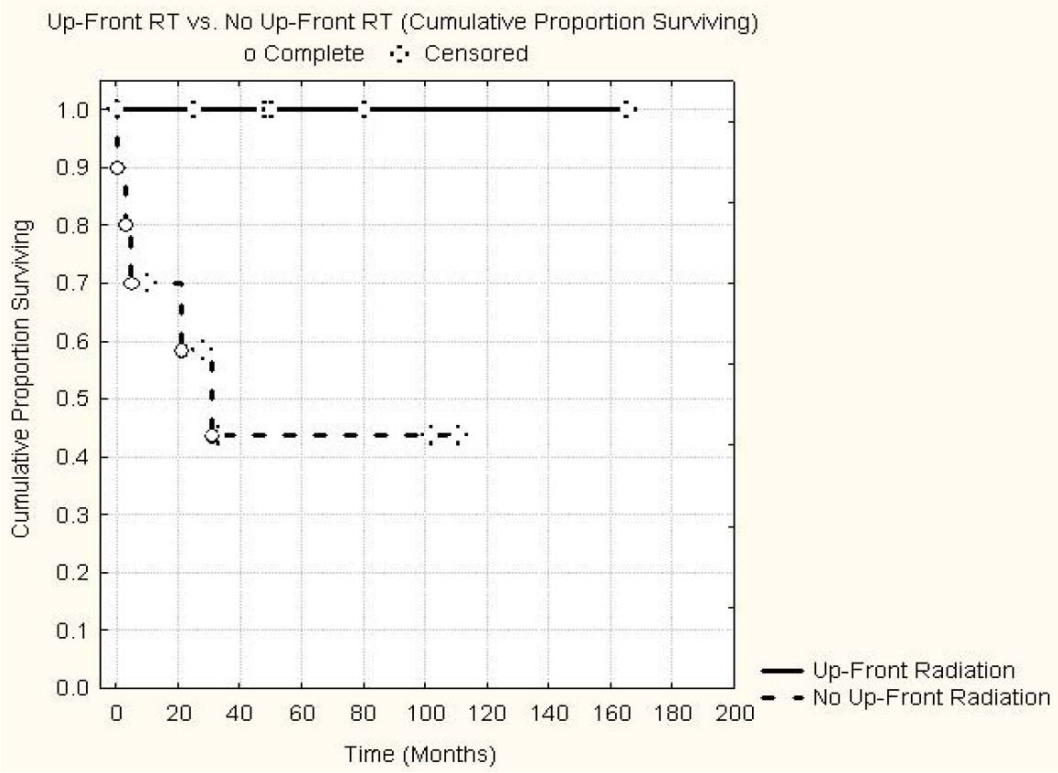

FIGURE LEGENDS

Figure 1: Overall survival according to whether patients did or did not receive radiation therapy as a component of initial treatment.